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CERTIFICATE OF MAILING

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ELI LILLY AND COMPANY

By KSRhoades Date 4-24-03

**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicant: Mark Brader, *et al.* | |
| Serial No.: 08/484,542 | |
| Filed: June 7, 1995 | Group Art Unit: 1631 |
| For: **Stabilized, Acylated Insulin Formulations** | Examiner: M. Allen |
| Docket No.: X-10097 | |

**DECLARATION OF MR. RICHARD A. BYRD UNDER 37 C.F.R. § 1.608(b)**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Richard A. Byrd declares as follows.

1. From 1981 to 2003, I have been employed as a toxicologist at Eli Lilly and Company. My current title is Research Scientist at Eli Lilly and Company. I received a Bachelor of Science degree from Harding University in 1974, and a Master of Science Degree in Interdisciplinary Toxicology from the University of Arkansas for Medical Sciences in 1981.

2. I am not a co-inventor in this application. The work I discuss in this Declaration is work done on behalf of the inventors on a compound called LY309132. LY309132 is

insulin that is acylated with palmitic acid (which is a 16 carbon fatty acid), at the epsilon amino group of lysine at position B29 of the insulin molecule. Thus, LY309132 is a fatty acid-acylated insulin molecule. In this Declaration, the terms "LY309132" and "C16-insulin" are used synonymously.

3. Exhibit 4 is a photocopy of the study plan for a dose ranging study with LY309132 in beagle dogs for which I was the study director and project leader. The study number was D06893. The original document was printed on September 16, 1993. As shown by my signature on the first page of the study plan, I approved the study plan on September 16, 1993. I confirm that the handwriting in the signature is mine.

4. As discussed in paragraph 5 of Exhibit 4, lot no. RS0163 (the reference standard lot) of LY309132 was to be used. As discussed in paragraph 6 of Exhibit 4, the first dose of LY309132 was to be 0.07 mg/kg animal weight. As discussed in paragraph 7 of Exhibit 4, LY309132 was to be administered subcutaneously to the animals.

5. Paragraph 8 of Exhibit 4 sets forth that a total of 6 animals would be used in the study, 3 male animals and 3 female animals. On the next to the last page of Exhibit 4, each animal was identified by animal number. Thus, the same set of animals was used for each dose administration. In the study plan, the start date was to be September 22, 1993, and the termination date was to be October 22, 1993, and the plan provided for a "wash-out" period of several days between doses, in order for each dose of LY309132 to be cleared from the animals before the next dose was given.

6. In paragraph 15 of Exhibit 4, it is shown that blood glucose levels were to be drawn from each animal at 0, 0.5, 1, 2, 4, 6 and 24 hours after each dose administration.

7. A 0.07 mg/kg dose of LY309132 was administered to each animal on September 22, 1993. Exhibit 5 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6 and 24 hours after the 0.07 mg/kg dose of LY309132 was administered. The original report was printed on September 24, 1993.

8. Exhibit 6 is a photocopy of Protocol Amendment No. 1. The original document was printed on September 24, 1993, and approved by me on the same date. In Exhibit 6, it is stated that an appropriate blood glucose response was shown with the initial dose administration (0.07 mg/kg) of LY309132, and that a second dose administration would be given to further define the hypoglycemic response. The study protocol was amended, such that each animal would receive a 0.11 mg/kg dose of LY309132.

9. On September 27, 1993, a 0.11 mg/kg dose of LY309132 was administered to each animal. Exhibit 7 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6, 8 and 24 hours after the 0.11 mg/kg dose of LY309132 was administered. The original report was printed on September 28, 1993.

10. Exhibit 8 is a photocopy of Protocol Amendment No. 2. The original was printed on September 30, 1993, and approved by me on the same date. In Exhibit 8, it is stated that a third dose administration would be given to further define the hypoglycemic response. The study protocol was amended such that each animal would receive 0.2 mg LY309132/kg on October 4, 1993.

11. On October 4, 1993, a 0.2 mg/kg dose of LY309132 was administered to each animal. Exhibit 9 is a photocopy of a Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after the 0.2 mg/kg dose of LY309132 was administered. The original report was printed on October 4, 1993 for all time points except for the 24 hour time point (first page of Exhibit 9), and the original report for the 24 hour time point was printed on October 6, 1993 (second page of Exhibit 9).

12. Exhibit 10 is a photocopy of Protocol Amendment No. 3. The original was printed on October 8, 1993, and approved by me on the same date. In Exhibit 10 it is stated that Phase IV [the fourth dose] would be conducted using 0.2 mg/kg of LY309132 with zinc (lot 2685-47A, which contained 0.023 mg of zinc oxide per vial).[1] The study protocol was amended such that each animal would receive 0.2 mg LY309132 with zinc/kg body weight.

13. On October 11, 1993, the 0.2 mg/kg dose with zinc was administered to each animal. Exhibit 13 is a photocopy of Clinical Pathology Interim Study Summary Report by J.A. Klepfer, which sets forth the glucose levels for samples that were collected from all six animals at 0, 0.5, 1, 2, 4, 6, 8, 10 and 24 hours after the 0.2 mg/kg dose of LY309132 with zinc

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[1] Exhibit 11 is a photocopy of an e-mail message to me from Mr. Dean Clodfelter, dated October 5, 1993, in which Mr. Clodfelter explains that lot 2685-47A was formulated with zinc, and that lot 2685-47A was made from bulk lot 487EM3 by Dr. Mark Brader. Exhibit 12 is a photocopy of an e-mail message from me to Dr. Brader, dated October 6, 1993, in which I confirmed receipt of zinc formulated C16 insulin.

was administered. The original report for all time points except for the 10 and 24 hour time points were printed on October 12, 1993 (first page of Exhibit 13). The original report for the 10 and 24 hour time points was printed on October 13, 1993 (second page of exhibit 13).

14. The data in Exhibit 13 show that the 0.2 mg/kg dose of LY309132 formulated with zinc exerted a hypoglycemic effect over time.

15. Exhibit 14 is a Summary of Study D06893 prepared on October 27, 1993 by Mr. N.R. Bernhard. As shown at the top of the Summary, I received a copy of the Summary. In the Summary, it is confirmed that the study had one treatment group containing three male and three female beagle dogs. It is also confirmed that there were four dosing phases, and that dosing occurred on September 22, September 27, October 4, and October 11, 1993 for Phases I, II, III and IV, respectively. It is also confirmed that Lot RS0163 was administered at 0.07, 0.11, and 0.2 mg/kg during Phases I, II, and III, respectively, and that 0.2 mg/kg of LY309132 containing zinc from lot 2685-47A was administered during Phase IV.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information of belief are believed to be true; and I am warned that all statements made herein were made with the knowledge that willful false statements are punishment by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful and false statements may jeopardize the validity of any patent issued from this application.

Richard A Byrd

April 21, ~~1003~~ 2003 RAB

Richard A. Byrd